Ethical and Regulatory Challenges for Human Environmental Research in the 21st Century

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Disclaimer

The views expressed in this presentation are my own and do not necessarily represent official positions of the U.S. Environmental Protection Agency or the U.S. Government

The State of Affairs at the End of the 20th Century

- The major domains of human environmental research
  - Controlled exposure research using non-vulnerable, non-susceptible subjects
  - Observational exposure research with non-vulnerable, non-susceptible subjects *and* vulnerable, susceptible subjects, principally children
  - Longitudinal epidemiological studies of the effects of naturally occurring environmental exposures
- The unresolved problem of research involving the intentional dosing of humans with pesticides to support pesticide registration applications

The State of Affairs at the End of the 20th Century

- The ethical and regulatory framework governing human environmental research in the United States
  - Human research conducted or supported by agencies of the Department of Health and Human Services (principally CDC and NIEHS) was regulated by the Common Rule plus additional protections for vulnerable groups in 45 CFR 46 Subparts B - D
  - Human research conducted or supported by EPA was regulated by the Common Rule alone
  - For both of the above, the Belmont principles served as the primary ethical foundation
  - Human research conducted and supported by third parties in support of pesticide registrations was unregulated

A Brief Ethical and Regulatory History of Human Pesticide Research

- The state of affairs prior to 1996
- The 1996 Food Quality Protection Act
- The response of third-party pesticide manufacturers
- The 1998 report of the Environmental Working Group
- The 2004 report of the National Academies
- The 2005 staff report prepared for Senator Boxer and Congressman Waxman
- The 2005 cancellation of the CHEERS study
- The 2006 Appropriations Act
- The 2006 revision of the EPA human studies rule

The 2006 Appropriations Act

- None of the funds…may be used by…the Environmental Protection Agency to accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until…final rulemaking on this subject.

- Such rule shall not permit the use of pregnant women, infants or children as subjects;…

The 2006 EPA Human Studies Rule

- Retains EPA's prior codification of the Common Rule (Subpart A)
- Adds three subparts (Subparts B-D) that incorporate prohibitions and additional protections for pregnant women, nursing women, and children in research conducted or supported by EPA
- Adds a series of subparts (Subparts K-Q) that include rules for third-party research for pesticides intended for submission to EPA under the pesticide laws

EPA's Subpart L

- Regulates third-party human research for pesticides involving the intentional exposure of pregnant women, nursing women, or children
- Defines *research involving the intentional exposure of a human subject* as the "study of a substance in which the exposure to the subject would not have occurred but for the subject's participation in the research"
- Categorically prohibits all research subject to this subpart

EPA's Subpart B

- Regulates research conducted or supported by EPA involving the intentional exposure of pregnant women, nursing women, or children
- Does not mention pesticides (or any other substances)
- Defines *research involving the intentional exposure of a human subject* exactly as in Subpart L
- Categorically prohibits all research subject to this subpart

EPA's Subpart B

- The prohibition on intentional exposure research is absolute and does not incorporate reference to either risk level or prospect of benefit, including direct benefit

- Research prohibited by Subpart B in pregnant women, nursing women, and children includes:
  - Intentional dosing human toxicity studies for pesticides
  - Pharmacokinetic studies at doses that produce no effect
  - Studies involving controlled exposures to neutral substances (such as clean, filtered air)
  - Nutritional studies involving the controlled administration of foods
  - Controlled studies of therapeutic substances, such as drugs

Ethical and Regulatory Challenges

- What are the ethical limits on the classes of substances to which children and other vulnerable subjects can be exposed under controlled conditions, and what are the ethical limits on the conditions under which such exposures can be permitted?

- How can an adequately protective new regulation be crafted that is consistent with the ethical analysis and with the statutory requirements mandated by Congress, yet does not impede ethically desirable research?

The Emerging Science of the 21st Century

- Expanded study of environmental exposures and their effects on individuals and populations in an era of environmental pollution and global climate change
- Interventional research to mitigate environmental exposures and their adverse effects at both the individual and the community level
- The science of gene-environment interactions
- Research on new technologies, such as nanotechnology

Case Study

- Examining exposure and health effects by environmental manipulation in a community setting
- Inhabited apartments randomly selected for treatment of cockroach infestations with different pesticide formulations and with integrated pest management
- Data on pesticide residues obtained from surface wipes
- Data on cockroach antigens obtained from dust samples

Ethical and Regulatory Challenges

- Traditional interpretations of the Common Rule would often not regard this as a human study on the grounds that the data are *about* the environment, not about living individuals

- Under what conditions is it ethically permissible to manipulate human environments for research purposes when living individuals are present while the effects of the manipulations are being felt *even if* no data will be obtained about them?

Ethical and Regulatory Challenges

- When can environmental data obtained when environments are manipulated for research purposes reasonably be considered to be *about* living individuals present in the environment while the effects of the manipulations are being felt?

- What are the ethical and regulatory considerations governing the possibility of adverse effects on individuals who are not themselves intended participants in the research?

Case Study

- Interventional research to mitigate environmental exposures at the community level
- Two water treatment approaches of uncertain relative effectiveness are compared between two communities
- Water-borne pollutants are measured at the taps in both communities
- Incidence of gastrointestinal disease is measured in the healthcare systems of both communities

Ethical and Regulatory Challenges

- What steps are ethically necessary for whole communities to be engaged in this kind of research?
- When is community consent morally valid if individual consent cannot reasonably be obtained?
- What kind of regulatory structure is necessary for this kind of research to go forward with adequate protection for all involved parties?
- Should this be permitted as research at all, or should it only be allowed in modified form as public health practice?

Beneath the Tip of the Iceberg

- How do we manage the privacy and confidentiality concerns arising from gene-environment interaction research?
- What research results should be returned to participants? When? To whom?
- What should be disclosed to participants if disclosure will alter the research results (Hawthorne effect)?
- What are the ethical and regulatory considerations governing the possibility of adverse effects of human research on the environment itself?

A Final Thought

“The significant problems we have cannot be solved at the same level of thinking with which we created them.”

- Albert Einstein